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Effect of M & B 17803A, a new β-adrenoceptor blocking agent, on the cardiovascular responses to tilting and to isoprenaline in man

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Summary

1. DL-1-(2-acetyl-4-*n*-butyramidophenoxy)-2-hydroxy-3-isopropylaminopropane hydrochloride (M & B 17803A) was given to four healthy volunteers in single oral doses of up to 300 mg. There were no subjective effects and no significant alterations in the heart rate, systolic and diastolic blood pressure in the seated position or in the forced expiratory volume or in the electrocardiogram within 6 h of the dose. There were no abnormalities in haematological tests and estimations of the serum glutamyloxaloacetic transaminase.

2. Oral doses of both M & B 17803A and propranolol inhibited the increase in heart rate which occurs on tilting from the supine to the 80° head up position. The results suggest that the degree of β-adrenoceptor blockade produced by M & B 17803A (100 and 300 mg) is comparable to that of propranolol (10 and 40 mg) respectively. Propranolol is 7·5–10·0 times as potent as M & B 17803A when compared by this method. There were no significant changes in the systolic or diastolic blood pressure after any of the treatments, in either of the positions studied.

3. M & B 17803A was also effective in inhibiting the increase in heart rate produced by the intravenous infusion of isoprenaline and in two subjects the degree of β-adrenoceptor blockade produced by M & B 17803A (300 mg) was comparable to that of propranolol (40 mg). M & B 17803A is a competitive β-adrenoceptor blocking agent and the duration of the pharmacological activity of both M & B 17803A and propranolol appeared to be very similar as assessed by this method.

4. In separate experiments with small oral doses of M & B 17803A no evidence of a selective action on myocardial β-adrenoceptors was obtained from the study of changes in heart rate and diastolic blood pressure (sphygmomanometric recording).

Introduction

DL-1-(2-acetyl-4-*n*-butyramidophenoxy)-2-hydroxy-3-isopropylaminopropane hydrochloride (M & B 17803A) is a new β-adrenoceptor blocking agent which is structurally related to both propranolol and practolol (Fig. 1). M & B 17803A blocks myocardial β-adrenoceptors in experimental animals but has a less marked action on β-adrenoceptors in bronchial and vascular smooth muscle (Basil, Jordan,

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Loveless & Maxwell, 1971) ; in this respect M & B 17803A resembles practolol, the only compound so far available which is a selective blocking agent of β-adrenoceptors in experimental animals (Barrett, Crowther, Dunlop, Shanks & Smith, 1968 ; Dunlop & Shanks, 1968) and in man (Brick, Hutchinson, McDevitt, Roddie & Shanks, 1968 ; Harrison & Turner, 1969 ; Powles, Shinebourne & Hamer, 1969 ; Palmer, Legge, Hamilton & Diament, 1969).

The objects of the work described here were: first, to assess the general tolerance of M & B 17803A in man after oral administration ; second, to study the β-adrenoceptor blocking activity of M & B 17803A by measuring its effect on the cardiovascular responses to passive tilting (endogenous stimulation of β-adrenoceptors) and intravenous isoprenaline (exogenous stimulation of β-adrenoceptors)—in the latter experiments it was hoped to obtain evidence of a selective effect of M & B 17803A on myocardial β-adrenoceptors ; and finally, to establish the time course of the β-adrenoceptor blocking activity of M & B 17803A after single oral doses in comparison with propranolol.

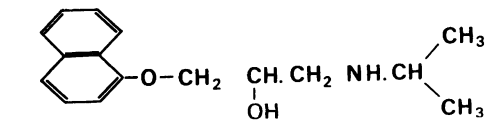
A preliminary report of this work has been presented to a meeting of the British Pharmacological Society (Cuthbert & Owusu-Ankomah, 1971).

Methods

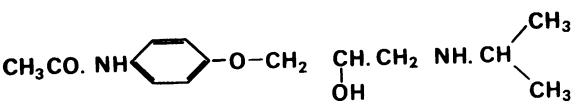
Experiments were performed in four healthy male subjects, aged between 24 and 40 years. None had any history of cardiac or respiratory disease and none was concurrently receiving any other drugs. The subjects were persons who by intelligence and training were able to appreciate the nature of the experiments.

Preliminary experiments

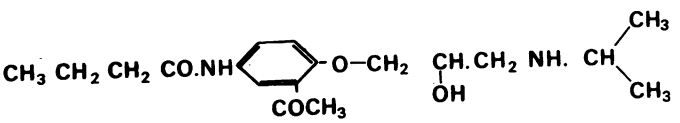
These were performed with the subject seated. The blood pressure was measured with a modified sphygmomanometer (Garrow, 1963 ; Dunne, 1969) by the same



Propranolol



Practolol (I.C.I.50.172)



M & B 17803A

observer. The heart rate was recorded by a pulse counter triggered by the electrocardiogram; the latter was displayed continuously on an oscilloscope. In all experiments three measurements of the blood pressure and pulse rate were made at 20 or 40 min intervals and the means calculated. The forced expiratory volume in one second (FEV_1) was measured with a dry bellows-type spirometer (Vitalograph) and the electrocardiogram recorded at 30 or 60 min intervals. Enquiry for subjective effects was made from a questionary at 30 or 60 min intervals.

Postural reflexes

The subject was placed in the supine position on a motor driven tilt table which incorporated a foot rest and rested for approximately 3 minutes. The heart rate was calculated from 30 s counts and the blood pressure measured, 3 times at 30 s intervals both in this position and the 80° head up position after allowing 2 min for stabilization. The procedures were then repeated. At each time interval the means were calculated for two sets of observations with the subject in the supine position and two sets of observations with the subject in the near-vertical position.

Isoprenaline-induced tachycardia

The subject rested on a couch with a comfortable back rest. A butterfly needle, gauge 19 or 21 (Abbott) was introduced into a suitable forearm vein and isotonic saline containing 1,000 units of heparin sulphate/500 ml was infused under hydrostatic pressure. The rate of the infusion was kept constant at 15 drops/min during the observations and discontinued only during the infusion of isoprenaline. A motor-driven infusion pump containing isoprenaline hydrochloride (expressed as base) in isotonic saline was connected to the system through a three-way tap. The duration of each infusion of isoprenaline was 30 s and the different doses achieved by varying the infusion volume from 0·1125–0·45 ml and by changing the concentration of the solution (range 10–100 μg/ml). Very occasionally, an infusion of 0·9 ml was required in order to deliver 90 μg, the maximum dose of isoprenaline used in any of these experiments. Ascorbic acid (200 μg/ml) was added to all solutions of isoprenaline. Under these conditions increases in the heart rate of 10–45 beats/min were achieved in the untreated subject with infusions of isoprenaline in the range 1·125–9 μg.

The increase in heart rate due to each isoprenaline infusion was calculated from a rate meter triggered by the R-R interval of the electrocardiogram which was displayed continuously. Measurements of the systolic and diastolic blood pressure were made at 1 min intervals using the modified sphygmomanometer (1 mmHg≡ 1·333 mbar). Neither the person measuring the blood pressure nor the subject was aware of the dose of isoprenaline infused or the oral treatment given.

Drugs

Gelatin capsules of identical appearance containing 2 mg, 10 mg, 25 mg, 100 mg and 300 mg of M & B 17803A or lactic acid, were supplied by May & Baker Ltd. Gelatin capsules containing 10 mg and 40 mg of propranolol and 50 mg of practolol were supplied by I.C.I. Pharmaceuticals Division. The propranolol and practolol capsules were also of identical appearance and these were similar to but not identical with the capsules of M & B 17803A. Solutions for intravenous infusion were pre-

pared from: isoprenaline hydrochloride, 1 mg/ml (Sustcardia, Pharmax Ltd.); heparin sulphate, 1,000 units/ml (Evans), and ascorbic acid, 50 mg/ml (Redoxin, Roche Products Ltd.).

Results

Preliminary experiments

Three healthy males received single oral doses of M & B 17803A selected from the following: 2 mg, 10 mg, 25 mg, 100 mg and 300 mg. There were no significant changes in the pulse rate, systolic or diastolic blood pressure in the seated position, or in the forced expiratory volume in 1 s (FEV_1) or in the electrocardiogram observed over 6 h after M & B 17803A (300 mg) was given by mouth. In these experiments the opportunity was taken to determine oral doses of M & B 17803A which produced an inhibition of the increase in heart rate due to tilting.

Venous blood samples were taken for full blood counts and serum glutamyloxaloacetic transaminase (SGOT) estimation both before and several hours after each oral dose. The initial blood counts and SGOT estimations were normal and no abnormality was detected on repeat estimations. After the human pharmacological studies were completed, each of the four subjects again received a single oral dose of M & B 17803A (300 mg) and blood counts and SGOT estimations were performed immediately before, 24 h after, and 6 days after the oral dose. No abnormalities were detected and there were no trends to suggest that this single dose had produced any adverse effect.

Comparison of M & B 17803A and propranolol on the cardiovascular responses to passive tilting

A comparison was made between the effect of M & B 17803A (100 mg), M & B 17803A (300 mg), propranolol (10 mg), propranolol (40 mg) and placebo on the increase in heart rate and the changes in blood pressure which occur when a subject is tilted from the supine to the 80° head up position. Three subjects received five different treatments on five separate occasions. One other subject received only M & B 17803A (300 mg), propranolol (40 mg) and placebo. The treatments were administered blind and the order of administration was randomized. Each subject received only one treatment on any 1 day and each experiment lasted approximately 7 hours. At least 7 days elapsed between any two treatments in each subject. The subjects took a normal breakfast on the day of the experiment and no food was then allowed until approximately 3 h after the oral dose.

There were no significant changes in the systolic or diastolic blood pressure produced by either dose of M & B 17803A or propranolol as compared with the placebo in either the supine or in the 80° head up position. After the administration of the placebo (Fig. 2), the heart rate in both the supine and upright positions was reduced during the first few hours of the experiment and increased during the latter half, but the increase in the heart rate produced by tilting remained relatively constant at each time interval. The lower doses of both M & B 17803A and propranolol produced a modest reduction in the tachycardia produced by tilting (Figs. 3 & 4; upper figures) but this was not statistically significant. In contrast, both M & B 17803A (300 mg) and propranolol (40 mg) caused a marked reduction in the tachycardia produced by tilting (Figs. 3 & 4; lower figures) and this was significant ($P<0.05$, Student's t

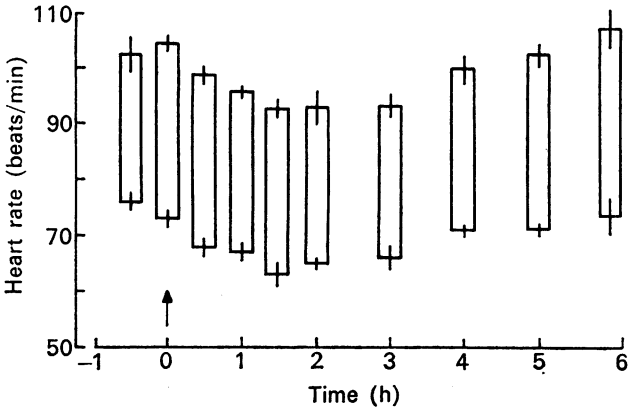


FIG 2. Effect of a placebo on the reflex increase in heart rate produced by tilting in four healthy males. The upper limit of each bar represents the mean heart rate when the subjects were in the 80° head up position and the lower limit represents the mean heart rate in the supine position. Vertical lines represent the standard error of the means. The placebo was given orally at the arrow.

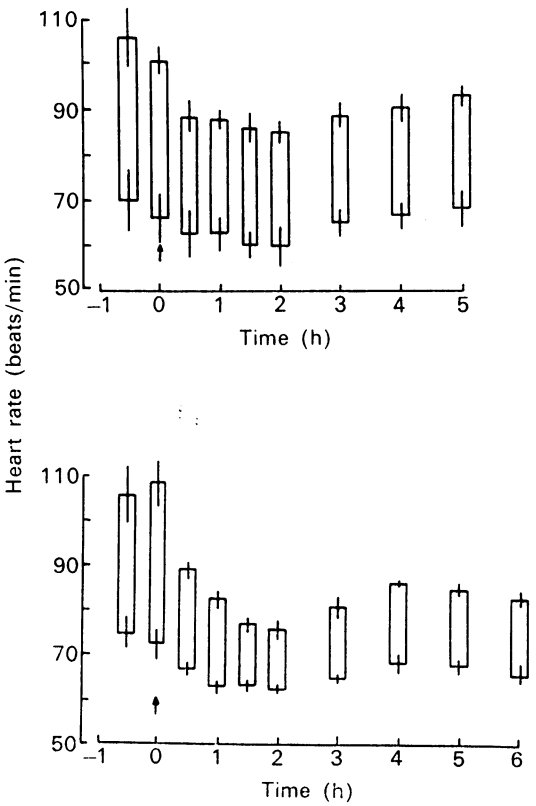


FIG. 3. Effect of M & B 17803A on the reflex increase in heart rate produced by tilting. The upper figure represents results obtained from three healthy males and the lower figure results obtained from four healthy males. The upper limit of each bar represents the mean heart rate when the subjects were in the 80° head up position and the lower limit represents the mean heart rate in the supine position. Vertical lines represent the standard error of the means. At the arrow 100 mg M & B 17803A (upper figure) or 300 mg M & B 17803A (lower figure) were given orally.

test for paired observations) at all time intervals from 30 min to 360 min inclusive after the oral dose of M & B 17803A (300 mg) and from 30 min to 90 min inclusive and again at 300 min after the oral dose of propranolol (40 mg). All statistical comparisons were made with the response to placebo at the appropriate time interval.

The peak effect of the higher dose of both M & B 17803A and propranolol appeared at 90–120 min and the results suggested that the duration of action of a single oral dose of M & B 17803A (300 mg) may be longer than that of propranolol (40 mg).

The maximum inhibition of the tilt-induced tachycardia produced by the low and high doses of propranolol was comparable to that produced by the corresponding doses of M & B 17803A. Dose-response lines were constructed, these were approximately parallel and showed that propranolol is 7·5 times more active than M & B 17803A, after oral administration in healthy subjects.

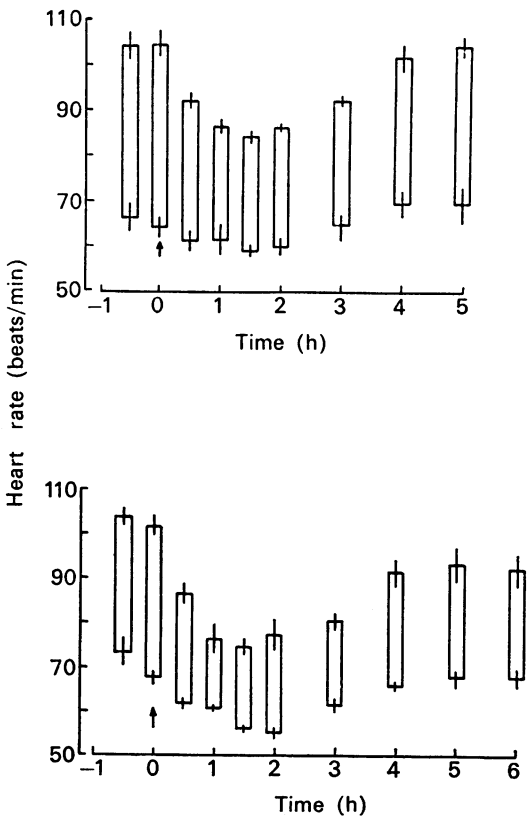


FIG. 4. Effect of propranolol on the reflex increase in heart rate produced by tilting. The upper figure represents results obtained from three healthy males and the lower figure results obtained from four healthy males. The upper limit of each bar represents the mean heart rate when the subjects were in the 80° head up position and the lower limit represents the mean heart rate in the supine position. Vertical lines represent the standard error of the means. At the arrow 10 mg of propranolol (upper figure) or 40 mg propranolol (lower figure) were given orally.

Comparison of the effect of M & B 17803A and propranolol on the cardiovascular responses to intravenous isoprenaline

In preliminary experiments single oral doses of M & B 17803A (100 mg and 300 mg) were highly effective in inhibiting the increase in heart rate and the changes in blood pressure produced by intravenous isoprenaline (2·25–9 μg) in three healthy volunteers; these responses were usually completely abolished 60–90 min after an oral dose of 300 mg.

To investigate the duration and extent of the β-adrenoceptor blocking action of M & B 17803A, two types of experiment were carried out. In the first, log dose curves were determined for the effect of intravenous isoprenaline on the heart rate in two healthy subjects. M & B 17803A (300 mg) or propranolol (40 mg) were then given by mouth and at each time interval the doses of isoprenaline which restored the responses to those found in the control period were determined, as described by Paterson, Conolly & Dollery (1970). In all cases dose-response curves were obtained (Fig. 5) which were parallel to each other and to the control dose-response curve. The degree of β-adrenoceptor blockade at each time interval after the oral administration of M & B 17803A or propranolol was calculated from the position of these curves as the ratio of the doses of isoprenaline required to produce an increase in heart rate of 25 beats/minute.

The results in one subject who took part in the first study are shown in Fig. 6. In both subjects the degree of β-adrenoceptor blockade produced by M & B 17803A (300 mg) and propranolol (40 mg) was very similar. Approximately 15 times the dose of isoprenaline was required to restore the responses in the first subject and approximately 30 times the dose of isoprenaline was required in a second subject. In both subjects there were differences in the onset and peak duration of β-adrenoceptor blockade, since the peak effect of M & B 17803A was evident at 2 h whilst that of propranolol was maximal at 1 hour. In both subjects the intensity of β-adrenoceptor blockade 6 h after drug administration was greater after M & B 17803A than after propranolol. In the subject in whom the responses to iso-

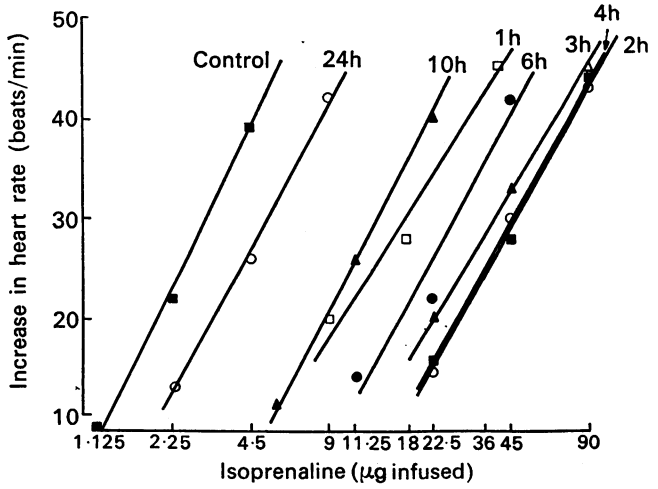


FIG. 5. Dose dependent increases in heart rate produced by the intravenous infusion of isoprenaline in a healthy male, wt. 85 kg, before and at various time intervals after a single oral dose of 300 mg M & B 17803A.

prenaline were followed for 24 h, the β-adrenoceptor blocking effect of the two drugs was identical at 10 h and 24 h after drug administration (Fig. 6). During this phase of the decline of the antagonism of the isoprenaline-induced tachycardia, the time for the antagonism to be reduced by one-half was approximately 10 h for both drugs.

In the second study an attempt was made to detect possible cardioselective properties of M & B 17803A on myocardial β-adrenoceptors in comparison with practolol by studying the effects of the drugs in antagonizing the tachycardia and fall

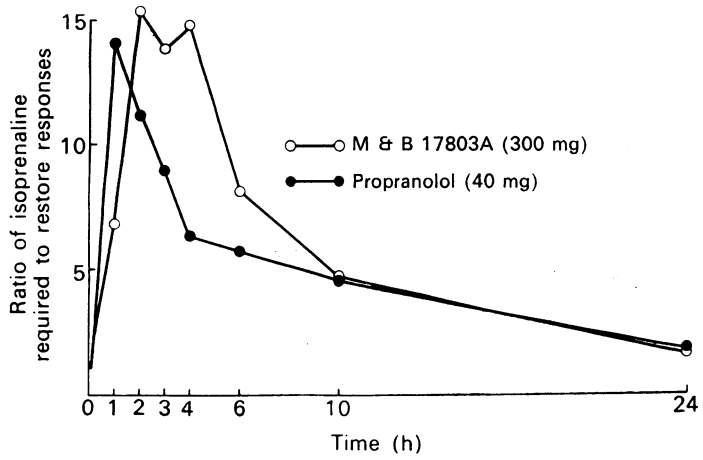


FIG. 6. The degree and duration of β-adrenoceptor blockade produced by a single oral dose of 300 mg of M & B 17803A or 40 mg of propranolol in a healthy male, wt 85 kg. The doses of isoprenaline required to produce increases in heart rate (12–45 beats/min) were determined before and at each time interval and the ratio calculated from the log dose-response curves.

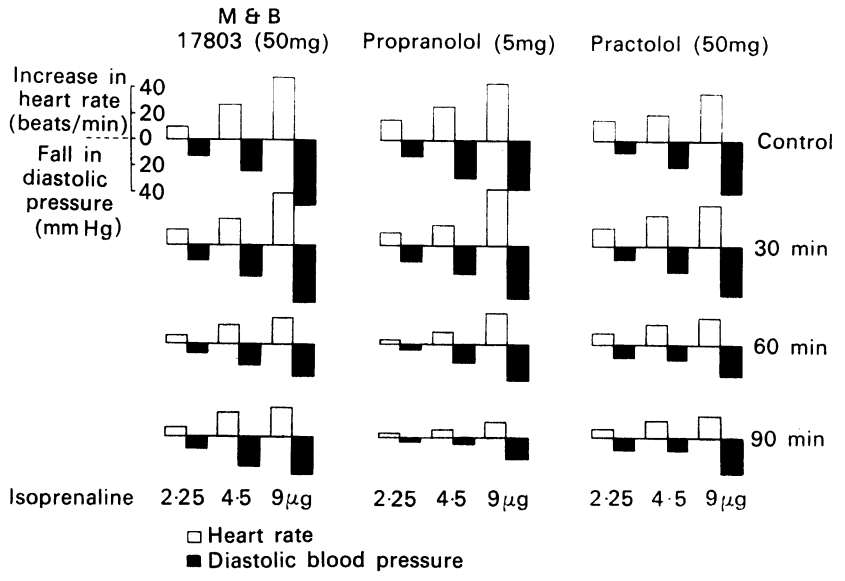


FIG. 7. Record of the changes in heart rate and diastolic blood pressure produced by intravenous isoprenaline before and at 30 min intervals after the oral administration of M & B 17803A, 50 mg, propranolol, 5 mg and practolol, 50 mg in a healthy male, wt. 69 kg.

in diastolic pressure produced by intravenous isoprenaline. Low doses of M & B 17803A (50–75 mg), propranolol (5–10 mg) and practolol (50 mg) were given orally to produce a gradual reduction in the isoprenaline-induced tachycardia. The results in one subject are shown in Fig. 7. These figures represent the maximum rise in heart rate and the maximum fall in diastolic blood pressure which occurred after intravenous infusions of isoprenaline in the doses indicated. Dose related effects for heart rate and diastolic pressure change were obtained before and at 30 min intervals after a β-adrenoceptor blocking drug had been given by mouth.

M & B 17803A, propranolol and practolol all caused a reduction in the increase in heart rate due to isoprenaline and there was a corresponding fall in diastolic blood pressure in each case. After each of the β-adrenoceptor blocking drugs, the reduction in the heart rate response was accompanied by a variable change in the diastolic pressure. Although at some time intervals after M & B 17803A and practolol there was some indication of a less marked inhibition of the fall in diastolic pressure than of the tachycardia as compared to propranolol, there were no consistent differences in the pattern of β-adrenoceptor blockade produced by M & B 17803A, propranolol and practolol. Similar results were obtained in two other subjects.

Discussion

The autonomic basis for the increase in heart rate which occurs when a subject is tilted from the horizontal to the near vertical head up position has been established by Robinson, Epstein, Beiser & Braunwald (1966). These authors showed that the main component of this reflex is mediated by stimulation of myocardial β-adrenoceptors. There is also a component due to inhibition of vagal parasympathetic activity. The modification of the tilting procedure used in this work has enabled equieffective doses of M & B 17803A and propranolol and their time courses of action to be determined.

After the administration of the placebo, the changes in the pulse rate in both the supine and the upright position were very similar in all four subjects. The changes in the heart rate recorded in the supine position are of particular interest since they are very similar to those which might be expected after the oral administration of single doses of β-adrenoceptor blocking agents. These findings stress the importance of including a placebo in studies on drugs which may influence the heart rate, especially when observations are made over several hours.

The study of the effect of M & B 17803A and propranolol on the increase in heart rate produced by intravenous isoprenaline has enabled the degree of β-adrenoceptor blockade produced by these compounds to be expressed quantitatively and information obtained on the onset and duration of action when single doses are given by mouth. The displacement of the log dose-response curve for isoprenaline on heart rate was parallel, which indicates that M & B 17803A, like propranolol (Paterson *et al.*, 1970) is a competitive β-adrenoceptor blocking agent. In doses which produced an equivalent degree of β-adrenoceptor blockade, the peak effect of M & B 17803A occurred at 2 h while that of propranolol occurred at 1 h ; the overall duration of action was very similar in the small number of subjects studied. It is encouraging that equivalent doses of these two drugs predicted from the study on tilting have been found to be equieffective using a method in which β-adrenoceptors are stimulated by exogenous isoprenaline rather than by endogenous catecholamines.

In an attempt to determine the selectivity of M & B 17803A on myocardial and peripheral vascular β-adrenoceptors, the changes in heart rate and blood pressure due to intravenous isoprenaline were studied both before and during β-adrenoceptor blockade. Similar studies have been performed with M & B 17803A in experimental animals (Basil *et al.*, 1971) and with practolol in experimental animals (Dunlop & Shanks, 1968) and in man (Brick *et al.*, 1968). In the experiments described here there was no obviously different action on myocardial and peripheral vascular β-adrenoceptors suggested for either M & B 17803A or practolol. These results may simply reflect the limitations of the method since changes in diastolic blood pressure are difficult to determine with any accuracy by sphygmomanometric methods. Other methods are necessary to determine whether M & B 17803A has, or has not, a selective action in man.

We should like to thank the subjects for consenting to take part in these studies, Dr. D. R. Maxwell and Dr. M. A. Rugg-Gunn of May & Baker Ltd. for supplies of M & B 17803A capsules, Dr. W. H. Jewell and Dr. R. A. Wiseman of Imperial Chemical Industries Ltd. for supplies of propranolol and practolol capsules, and Mr. A. K. Arora for technical assistance. Our thanks are also due to Dr. D. W. Vere for helpful criticism of the manuscript and to Dr. H. B. May for carrying out the haematological tests and SGOT estimations.

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